REMARKS

Applicants wish to thank the Examiner for her courtesy in the telephonic interview conducted on September 9, 2004.

The Examiner indicated that several papers are missing from the file. The Applicants are enclosing copies of the papers that they believe the Examiner is missing. If the Examiner would like copies of anything else that the Applicants have not enclosed please let the Applicants' representative know.

Claims 168-186 are pending. Claims 168-173, 177, and 179-185 have been amended. Claims 168 and 180-185 were amended to define "M" as a nucleoside. Claims 169-173, 177, and 179 were amended to clarify the term "MH."

Claim 186 is newly added. Support for new claim 186 can be found at p. 40 line 17- p. 41 line 40.

All pending claims stand rejected. The Examiner also notes that no prior art has been cited against the Applicants' claims.

All of the above changes are cosmetic and none raise any issue of patentability. Both before and after the above changes, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq*. The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents. Accordingly, under no circumstances whatsoever may these claims be interpreted as:

- having been altered in any way for any reason related to patentability;
- having been narrowed;

- a concession that the invention as patented does not reach as far as the original, unamended claim;
- a surrender of any subject matter as a condition of receiving a patent; and/or, estopping applicants from asserting infringement against every equivalent, whether now known or later developed, foreseen or unforeseen;

Applicants also emphasize that the decision to address the Examiner's suggestions via claim amendment with the understandings set forth above is not in any way intended to avoid the "gatekeeping" role of the PTO with regard to the examination and issuance of valid patents for patentable inventions.

I. 35 USC § 112 REJECTIONS

A. First Paragraph, Written Description

The Examiner has rejected claims 168-185 under 35 USC § 112, second paragraph as lacking written description. The Examiner states:

> The claims fail to comply with the written description requirement because of the variable M definition. In particular, the phrase 'M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active in vivo and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom with the proviso that M-PO_3^{2-} is not an FBPase inhibitor' (see independent claims 168 and 180-185) does not disclose what biologically active compounds the invention encompasses. There is/are not structure(s) to determine what agents Applicant are claiming to be compatible with the instant invention. The specification discloses limited exemplification of specific M species (i.e., M is the compound of formulae II (page 59), III (page 60), and IV (page 61), or a nucleoside (page 74, lines 13-25)) that are encompassed by the instant invention while the claims are directed to any and all possible biologically active agents. In addition, the specification and claims does not distinguish what are the FBPase inhibitors. Thus, since the specification and claims do not contain a clear and concise description, a written description rejection is proper. (Office Action pp. 2-3)

The Applicants respectfully traverse this rejection.

The Applicants have clearly shown that they were in possession of the invention. The Applicants made numerous prodrugs of this invention. (*see* Specification pp. 132-161) Additionally, Applicants have conducted numerous tests on compounds of this invention including: activation by rat and human liver microsomes (Exs. D and E); activation by recombinant CYP3A4 (Ex. G); and inhibition of glucose production in rat hepatocytes (Ex. J).

The claims say "M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom, with the proviso that M-PO_3^{2-} is not an FBPase inhibitor." M-PO_3^{2-} is defined by the functional limitation of "is biologically active *in vivo* ...with the proviso that M-PO_3^{2-} is not an FBPase inhibitor." Functional language in claims has long been considered acceptable. *See In re Swinehart and Sfiligoj*, 169 USPQ 226, 228 (C.C.P.A. 1971). MPEP §2173.05(g), discusses functional limitations, referring to *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971), where: "It was held that the limitation used to define a radical on a chemical compound as 'incapable of forming a dye with said oxidizing developing agent' although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought." A person of ordinary skill in the art can perform a standard assay to determine if an M compound satisfies the functional definition. A person of ordinary skill in the art would be able to determine what M compounds are claimed by the present invention.

Furthermore, as stated in the Declaration of Dr. Erion, "a person of ordinary skill in the art would understand what drugs are biologically active when attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$" [Erion Decl. para. 5] As explained by Dr. Erion, the term biologically active is defined in the specification at p. 21, lines 8-10. In addition:

> The specification also explains that "The present invention is directed towards novel prodrugs of phosphate, phosphonate, and phosphoramidate compounds which in their active form have a phosphate, phosphonate, or phosphoramidate group." (p. 1, lines 10-12) "The invention is directed to the use of new cyclic phosph(on)ate ester methodology which allows compounds to be efficiently converted to phosph(on)ate containing compounds by p450 enzymes found in large amounts in the liver and other tissues

containing these specific enzymes." (p. 22, lines 37-40) "This methodology can be applied to various drugs and to diagnostic imaging agents." (p. 22, line 40) Moreover, "The Background of the Invention" discusses numerous examples where the phosphates, etc. are biologically active. For example, the specification specifically discusses 3TC and araA:

A large class of drugs known to be active against hepatitis are generally nucleoside or nucleotide analogs that are phosphorylated inside cells to produce the biologically active triphosphate. Examples include Lamivudine (3TC) and Vidarabine (araA). p. 5, lines 16-18

The specification also defines the term "parent drug" and gives an example of how AZT-triphosphate is biologically active:

The term "parent drug" refers to MH for phosph(oramid)ates where M is connected to –P(O)(OR)(OR) via oxygen, sulfur, or nitrogen, and M-PO_3^{2-} when M is connected to –P(O)(OR)(OR) via carbon. For example, AZT can be thought of as a parent drug in the form of MH. In the body AZT is first phosphorylated to AZT-PO_3^{2-} and then further phosphorylated to form AZT-triphosphate, which is the biologically active form. The parent drug form MH only applies when M is attached via N, S or O. In the case of PMEA, the parent drug form is M-PO_3^{2-}. (specification p. 21, lines 1-7)

From the specification descriptions and the examples regarding 3TC, araA, and AZT, one of ordinary skill in the art is aware that the biologically active form of the compound is interacting with the receptor or enzymes such as viral or animal polymerases, for example. [Erion Decl. para. 7]

Clearly, "A person of ordinary skill in the art reviewing this specification can apply this technology to any M that is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo*. Applying the invention generally does not depend on the structure of M." [Erion Decl. para. 9]

However, in order to advance the prosecution, the Applicants have defined "M" in claims 168 and 180-185 as a nucleoside per the Examiner's suggestion during the interview of September 9, 2004.

In view of the above, the Applicants respectfully request that the Examiner withdraw the written description rejection.

B. Second Paragraph Indefinite

1. Claims 168-185

The Examiner has rejected claims 168-185 under 35 USC § 112, second paragraph as indefinite. The Examiner argues that the claims are ambiguous. The Examiner says:

> The claims as written are ambiguous because it is unclear what is encompassed by Applicant's variable M. Specifically, the phrase 'M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active in vivo and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom with the proviso that $M\text{-}PO_3^{2-}$ is not an FBPase inhibitor' (see independent claims 168 and 180-185) is confusing. In particular, it is unclear what biologically active compound(s) Applicant is claiming that are compatible with the instant invention. Is Applicant claiming all possible biological agents? What does Applicant mean by the phrase with the proviso that '$M\text{-}PO_3^{2-}$ is not an FBPase inhibitor'? What limitations/conditions has Applicant set forth to distinguish whether $M\text{-}PO_3^{2-}$ is not an FBPase inhibitor or not? Hence, it is unclear which compound(s) Applicant is excluding from the claim. Applicants is respectfully requested to clarify the claims in order that one may readily ascertain what is being claimed.

The Applicants respectfully traverse this rejection.

As explained above, the specification defines the term "biologically active drug or agent" as:

> refers to the chemical entity that produces a biological effect. In this invention, biologically active agents refers to $M\text{-}PO_3^{2-}$, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ where M can be the same M as in the parent drug or metabolite. (p. 21, lines 8-10)

"A person of ordinary skill in the art reviewing this specification can apply this technology to any M that is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo.* Applying the invention generally does not depend on the structure of M." [Erion Decl. para. 9] As stated in the Declaration of Dr. Erion, "a person of ordinary skill in the art would understand what drugs are biologically active when attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$" [Erion Decl. para. 5]

As stated in the Declaration of Dr. Erion "the determination of what is or what is not an FBPase inhibitor is a matter of routine screening and was a matter of routine screening by March of 1998. A person of ordinary skill in the art would be guided by the specification." [Erion Decl. para. 11] Furthermore, as explained by Dr. Erion:

> It is a matter of routine testing to determine whether or not a given compound is an FBPase inhibitor. For example, enzymatic activity is easily determined spectrophotometrically. By March of 1998 such a spectrophotometric analysis was easily and routinely accomplished. In addition, by March of 1998, High Throughput Screening allowed a rapid evaluation of large numbers of compounds. (1000s per day). [Erion Decl. para. 12]

Clearly, "Given the guidance in the specification and the routine nature of the testing involved, as of March 1998, a person of ordinary skill in the art can easily determine what compounds of formula M-PO_3^{2-} are not FBPase inhibitors and thus are excluded from the scope of the claims." [Erion Decl. para. 13]

However, in order to advance the prosecution, the Applicants have defined "M" 168 and 180-185 as a nucleoside per the Examiner's suggestion during the interview of September 9, 2004.

In view of the above, the Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

2. Claims 169-173, 177, and 179

The Examiner has rejected claims 169-173, 177, and 179 under 35 USC § 112, second paragraph as indefinite. The Examiner says:

> Claims 169-173, 177, and 179 recite the limitation "wherein MH is" in line 1. There is insufficient basis for this limitation in the claim.
>
> Did Applicant intend to write "wherein M is" instead of "wherein MH is"? (Office Action p. 4)

The Applicants respectfully traverse this rejection.

The Applicants did intend to use the term "MH." The Applicants note that the specification at p. 21, lines 1-7 explains the relationship of M and MH:

> The term "parent drug" refers to MH for phosph(oramid)ates where M is connected to –P(O)(OR)(OR) via oxygen, sulfur, or nitrogen, and M-PO_3^{2-} when M is connected to –P(O)(OR)(OR) via carbon. For example, AZT can be thought of as a parent drug in the form of MH. In the body AZT is first phosphorylated to AZT-PO_3^{2-} and then further phosphorylated to form AZT-triphosphate, which is the biologically active form. The parent drug form MH only applies when M is attached via N, S or O. In the case of PMEA, the parent drug form is M-PO_3^{2-}.
> (specification p. 21, lines 1-7)

MH clearly refers to the parent drug. The parent drug MH is phosphorylated to become the biologically active drug. (*see* specification pp. 37-38).

Given the teaching in the specification, a person of ordinary skill in the art would not find the claims ambiguous and would have no difficulty in determining the scope of the claims. However, in order to advance the prosecution of this application the Applicants have amended the claims to read "wherein M attached to H."

In view of the above, the Applicants respectfully request that the Examiner withdraw the indefiniteness rejection.

CONCLUSION

In view of the foregoing remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

As discussed during the interview on September 9, 2004, the Examiner is invited to contact the undersigned if it will help to further clarify any issue within this Response.

Respectfully submitted,

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By: Diana L. Bush

Diana L. Bush, Ph.D.
Reg. No. 51,109

PAUL, HASTINGS, JANOFSKY & WALKER LLP
3579 Valley Centre Drive
San Diego, CA 92130
Telephone: (858) 720-2500
Facsimile: (858) 720-2555